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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,311	11/20/2003	John A. Chiorini	14014.0252U3	3284

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
09/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/719,311	**Applicant(s)** CHIORINI ET AL.	
	Examiner Sumesh Kaushal	**Art Unit** 1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 19 June 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *2-3, 6-28, 30-36, 38-42*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Sumesh Kaushal/
Primary Examiner, Art Unit 1633

Continuation of 3. NOTE: Newly filed claim 43 would require additional search and/or consideration.

Continuation of 11. does NOT place the application in condition for allowance because:

Claims 2-3, 6-28, 30-36 and 38-42 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reason of record as set forth in the office action mailed on 03/21/08.
The applicant argues that according to new written description guidelines (Example 11A) the invention as claimed meets written description requirements. The scope instant claims encompasses a vector system that comprises variants of AAV4 capsid protein and AAV4 Rep protein. However applicants arguments are found not fully persuasive because the invention as claimed in claim 2 in the instant applicantion recites a variant with a specific function and the specification as filed fails to disclose any variant that has the claimed functional properties (i.e. formation of transducing AAV particles) with respect to 15% variation in SEQ ID NO:4. Contrary to applicant's assertion, the specification on page 2 clearly teaches "Deletion analysis has shown that removal or alteration of VP1 which is translated from an alternatively spliced message results in a "reduced yield of infections particles". Mutations within the VP3 coding region result in the "failure to produce any single-stranded progeny DNA or infectious particles". Therefore even in view of the state of the art (spec page2), the specification fails to further disclose any Capsid or Rep variants that have the ability to form transducing AAV particles.

Claims 2-3, 6-28, 30-36 and 38-42 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vector system for producing infectious AAV4 particles comprising AAV4 capsid proteins (SEQ ID NO: 4, 16 and 18) and AAV4 Rep proteins (SEQ ID NO:2, 8, 9, 10 and 11), does not reasonably provide enablement for any other vector system that comprises any variant of AAV4 Capsid (i.e. SEQ ID NO: 4, 16 and 18) or Rep proteins (i.e SEQ ID NO:2, 8, 9, 10 and 11) and/or any vector system that only encodes a single Capsid or Rep protein and is capable of producing the AAV particles. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the reason of record as set forth in the office action mailed on 03/21/08.
The applicant argues that the skilled artisan is guided by the specification and knowledge in the art for AAV2 to make modifications to capsid sequence that would result in a transducing particle by i) conserving residues demonstrated to be important for AAV2 and ii) conserve residues that are consistent between AAV2 and AAV4. The applicant argues that the information available in the art combined with the general predictability for maintaining function at sequence identities above 70% is such that the skilled artisan would be able to design a capsid protein having 90% sequence identity to the disclosed sequence for AAV4 capsid that is capable of assembling into a transducing viral particle. However this is found not persuasive in view of "written description" rejection above as the specification fails to disclose varaints defined by structure and function, which one skilled in the art would be able to use form AAV particles without furhter undue amount of experimentation. Furthermore the applicant fails to consider the scientific reasoning that screening of any and all natural and non-natural variants, wherein at least 10% of residues are added substituted and/or deleted at random in the disclosed SEQ ID NO(s) is not considered routine in the art, especially in view of applicants own disclosure that clearly teaches spec. page 2 para.2 that "Deletion analysis has shown that removal or alteration of VP1 which is translated from an alternatively spliced message results in a "reduced yield of infections particles". Mutations within the VP3 coding region result in the "failure to produce any single-stranded progeny DNA or infectious particles". The specification fails to disclose any Capsid or Rep variants that have the ability to form transducing AAV particles. Furthermore, making and testing a point mutation is significantly different from the making and testing an amino acid sequences wherein at least 10% amino acids are added, deleted and/or substituted. The number of possible scenario increase geometrically with increase in percent non-identity. Such making and testing is nothing more than an invitation to further undue experimentation, since the specification can not be relied on to teach how to make the variants as claimed (see Spec. page 2 para.2). The variation as claimed also encompasses the conserved motifs that are germane to native biological activity (i.e. formation of AAV particles) of the encoded protein. It is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. The applicant has not presented enablement commensurate in scope with the claims. Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. This is not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. .